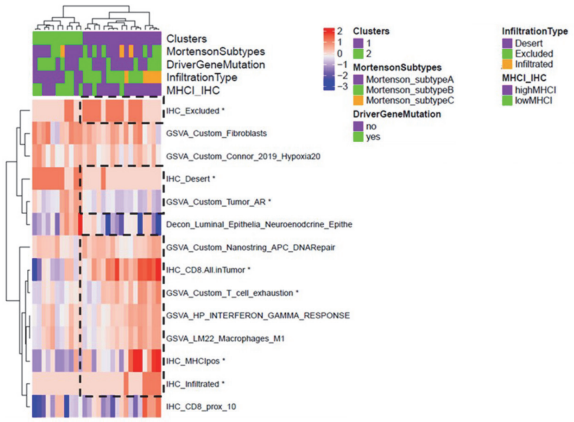

Abstract 733 Figure 1 Unsupervised analysis of primary hgPCa that develop metastasis. Features used for unsupervised classification into Cluster 1 and Cluster 2 are: IHC CD8+ cell proximity to tumor cells (IHC_Infiltrated/Desert/Excluded), CD8+ overall cell density in tumor area, MHCI IHC H-score in tumor (% of tumor cells that are positive X stain intensity), RNAseq signatures for AR pathway in tumor, T-cell exhaustion, Interferon-γ, Macrophage M1, Neuroendocrine phenotypes and DNA repair pathway. Patient cohort annotated for at least one mutations in driver genes (TP53, RHPN2, KMT2D), percent tumor expression of MHCI IHC (>25% high, <25% low), CD8 infiltration type in relation to tumor and cancer subtypes as defined by Mortensen mRNA profiling (Mortensen at al, Science Reports 2015).

compared to lgPCa. Assessment of MHC-I deficiency by IHC and mRNA revealed that hgPCa has significantly lower MHC-I protein expression compared to lgPCa. Interestingly, MHC-I loss in hgPCa associated with a T-cell exclusion phenotype. Moreover, RNAseq gene expression signatures revealed higher expression of tumor-associated macrophage (TAMs), T-regs, Cancer-Associated Fibroblasts (CAFs), DNA damage repair (DDR) genes and lower Interferon-γ (IFN- γ) expression in hgPCa compared to lgPCa. Overall, hgPCa is characterized by a combined phenotype of 'MHCIloss/IFN- γ low/CAFhigh/TAMhigh/T-reghigh/DDRhigh'. 2.Comparisons within hgPCA that develop metastasis: Unsupervised analysis of molecular features in hgPCa patients that developed metastases identified a subset of patients that exhibit a less immunosuppressive phenotype with lower tumor AR expression, retained tumor MHC-I expression, moderate CD8+ T-cell infiltration and a high IFN-γ RNA signature (figure 1), suggesting potential benefit from ICB therapy

Conclusions Our analysis suggests that hgPCa is characterized by low antigenicity as assessed by loss of MHC-I protein expression and an immunosuppressive microenvironment rich in CAFs, macrophages, T-regs and T-cell exclusion phenotypes. Unlike lgPCa, hgPCA can have a poor prognosis (within 5 years relapse). However, a subset of hgPCa patients that metastasized while on SOC exhibited a biomarker profile that might benefit from combination of SOC with ICB

Ethics Approval This study was approved by BMS Cambridge Massachusetts Institutional Biosafety Committee, approval number CAM_2020_12050_6

Consent 'Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.'

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0733

734 A NOVEL NQO1 SPECIFIC ANTI-TUMOR AGENT, SBSC-S3001, SELECTIVELY REGRESSES THE GROWTH OF TUMORS WITH HIGH NQO1 EXPRESSION

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Background NAD(P)H-quinone oxidoreductase 1 (NQO1) is a cytosolic two-electron oxidoreductase overexpressed in many types of cancers, including breast cancer, pancreatic cancer, colorectal cancer, cholangiocarcinoma, uterine cervical cancer, melanoma, and lung cancer.[1]Up-regulation of NQO1 protects cells from oxidative stress and various cytotoxic quinones and is associated with late clinical stage, poor prognosis and lymph node metastasis.[2] [3] NQO1 increases stability of HIF-1α protein, which has been implicated in survival, proliferation, and malignance of cancer.[1] Therefore, accumulating evidences suggest NQO1 as a promising therapeutic target for cancer. Accordingly, we have characterized the effect of a novel synthetic NQO1 substrate SBSC-S3001, and demonstrated its selective cytotoxic effects in cancer cells with high expression of NQO1.

Methods In vitro cytotoxicity was determined by sulforhodamine B (SRB) assay in cancer cells with high NQO1 expression and CRISPR-mediated NQO1 knockout cells. The effect of SBSC-S3001 on the energy metabolism pathway was evaluated by western blot analysis of metabolism associated proteins from NQO1-overexpressed cancer cells treated with the compound for 24 hours. In vivo anti-tumor activity was evaluated in MC38 syngeneic and DLD-1 orthotopic mice models.

Results SBSC-S3001 exhibited selective cytotoxicity in cancer cells with high expression of NQO1 in a dose-dependent manner. The cytotoxicity was observed in both normoxia and hypoxia conditions, correlating with the energy metabolism, mitochondrial biogenesis, and cancer proliferative pathways. Also, stronger cytotoxicity was observed in NQO1-overexpressed cancer cells treated with SBSC-S3001 compared to beta-lapachone and analogue treatment.[4] When evaluated in vivo, SBSC-S3001 effectively inhibited the growth of syngeneic and orthotopic tumors when administered as a monotherapy. SBSC-S3001 treatment associated with reduction in key enzymes of the glycolytic pathway (LDHa and GAPDH) and HIF-1α and increase in levels of mitochondrial oxidative phosphorylation (OXPHOS) complex.

Conclusions Treatment of SBSC-S3001, a novel, NQO1-specific substrate reduces HIF-1α and key enzymes associated with glycolysis and suppresses the growth of tumors overexpressing NQO1. Further characterization of SBSC-S3001 as a novel metabolic anti-cancer agent for cancers with NQO1 overexpression is warranted.

Ethics Approval The study was approved by Samyang Biopharmaceuticals Institution's Ethics Board, approval number SYAU2031.

REFERENCES

1. Oh ET, Kim JW, Kim JM *et. al*., NQO1 inhibits proteasome-mediated degradation of HIF-1α. *Nat Commun* 2016; **14**:13593.
2. Ma, Y. *et al*. NQO1 overexpression is associated with poor prognosis in squamous cell carcinoma of the uterine cervix. *BMC Cancer* 2014;**14**: 414
3. Yang, Y. *et al*. Clinical implications of high NQO1 expression in breast cancers. *J. Exp. Clin. Cancer Res* 2014;**33**:144.
4. Yang Y, Zhou X, Xu M, *et al*., β-lapachone suppresses tumour progression by inhibiting epithelial-to-mesenchymal transition in NQO1-positive breast cancers. *Sci Rep* 2017;**7**:2681.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0734